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EXAMINER	
JOHANNSEN, DIANA B	

ART UNIT	PAPER NUMBER
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/880,732	BEE ET AL.	
	Examiner	Art Unit	
	Diana B. Johannsen	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6,9 and 59-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9 and 59-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. It is again noted that the finality of the Office action of February 9, 2007 has been withdrawn (see the Notice of Panel Decision mailed September 24, 2007). Prosecution has been reopened, and new grounds of rejection are set forth below. Any rejection not reiterated herein has been withdrawn. This action is **NON-FINAL**.

2. Claims 1-6, 9, and 59-71 remain pending and are now under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6, 9, and 59-71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

In the Amendment filed April 5, 2006, Applicants amended claim 1 so as to include the limitation "using white light, with the proviso that the white light is not evanescent wave light." The originally filed specification does not provide basis for this limitation. As discussed in MPEP 2173.05(i), "Any negative limitation or exclusionary proviso must have basis in the original disclosure," and "Any claim containing a negative limitation which does not have basis in the original disclosure should be rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description

requirement." In the instant case, the specification does refers to methods that "use illumination with non-evanescent wave light" (see page 11, lines 8-9), and it is also noted that original claim 36 disclosed methods in which "said illuminating is with non-evanescent wave light." However, the originally filed specification does not make reference to the use in applicants' methods either of white light in general or of white light "with the proviso that the white light is not evanescent wave light." In describing the characteristics of the "scattered light detectable particles" employed in applicants' methods, the specification does teach that the particles exhibit certain properties "on illumination with white light" (see page 5, lines 22-26). Additionally, applicants disclose that particles included in their kits may produce "different colors of scattered light on illumination with polychromatic light, such as white light" (page 12, lines 21-23). However, there is again no disclosure of "white light, with the proviso that the white light is not evanescent wave light;" applicants' particles are described by reference to "white light" and "polychromatic light, such as white light." Thus, the specification provides a general disclosure of the use in applicants' methods of any "non-evanescent wave light," and a separate general disclosure of particles that have certain properties upon illumination with white light. With regard to the methods exemplified in applicants' specification, it is noted that applicants do not specify the type of illumination employed therein; rather, the specification merely indicates that "the illumination source and the detector or detectors are configured to reduce background signal so that a sensitive assay results" and that "a signal is obtained from the RLS particles by measuring light scattering" (page 45, lines 9-10, and 27-28); and states that spots "are visualized" (page

50, line 7). Thus, neither the general teachings of the specification nor the examples set forth therein provide basis for a step of illuminating in which the particular species of light "white light, with the proviso that the white light is not evanescent wave light" is employed. Accordingly, Applicants' amendment introduces new matter.

It is noted that the Pre-Appeal Brief Request for Review filed August 9, 2007 traverses the rejection on the following grounds. The Request argues that the Office appears to be requiring *ipsis verbis* support although such support is not required. Applicants argue that "the specification as filed would allow one of ordinary skill in the art to recognize or visualize the presently claimed invention," referencing the teachings noted above at pages 11 and 12. The Request argues that the specification "states that, without limitation, non-evanescent wave light can be used to illuminate" (reference paragraph 56/page 12) and "that white light, without limitation, can be used to illuminate" (paragraph 46/page 11). Applicants conclude that thus "the specification specifically teaches the use of white light and non-evanescent light."

These arguments have been thoroughly considered but are not persuasive. The examiner agrees that the specification teaches methods employing non-evanescent wave light, and discloses particles that have particular properties when illuminated with white light. However, as discussed above, there is no disclosure in applicants' specification, be it express, implicit, or inherent, of a method in which the particular type of light now recited in the claims is employed. While the Request asserts that white light illumination has been disclosed "without limitation," the only context in which white light is discussed in the specification is with reference to the type of particles that may be

employed in applicants' methods and packaged in applicants' kits, and the characteristics those particles have when illuminated with white light. The use of white light in the "illuminating" step of applicants' methods is not disclosed, nor do applicants' Examples give any indication of the type of light actually employed therein. Thus, the specification as originally filed would not in fact allow one of ordinary skill in the art to recognize or visualize the invention now claimed.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 1-6, 9, and 59-71 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-6, 9, and 59-71 are indefinite because it is not clear how the method steps of claim 1 relate to one another and to the objective of "detecting specifically an allele of a pharmacogenetically relevant gene involved in drug metabolism in a sample" (see preamble of claim 1). It is noted step (c) of the claim recites a step of detecting light "as indicative of the presence of said allele in said sample." However, step (a) of the claim merely requires contacting the sample with a probe under conditions that allow the probe "to hybridize specifically to a nucleic acid molecule in said sample, wherein said nucleic acid molecule comprises a target sequence." Step (a) does not, e.g., refer to "said target sequence" (i.e., refer back to the particular target sequence of the claim preamble), and there is no other indication or requirement in step (a) that

either the probe or the nucleic acid molecule have a relationship with the "allele" or target sequence "unique to" the allele that are previously and subsequently mentioned in the claim. Clarification is therefore required with regard to how the "contacting" and subsequent "illuminating" of steps (a) and (b) result in allele detection as required by the claims.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

9. Claims 1-3, 5-6, and 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al (US 6,045,996 [4 April 2000; filed 16 May 1996]) in view of Yguerabide et al (Analytical Biochemistry 262:137-156 [1998]).

Cronin et al disclose array-based methods for differentiating alleles of CYP2D6 (see entire reference, particularly the Example at col 10, line 47-col 11, line 20). It is a property of CYP2D6 that it is a "pharmacogenetically relevant gene involved in drug metabolism," as required by the claims; note, e.g., the text of claim 70, which states that "the pharmacogenetically relevant gene involved in drug metabolism encodes a cytochrome P450 protein," and the text of claim 71, which requires that "the pharmacogenetically relevant gene involved in drug metabolism is a member of the CYP2D family." Further, Cronin et al disclose target sequences unique to various CYP2D6 alleles, and (with particular regard to step (a) of claim 1) disclose contacting samples with arrays comprising probes that hybridize specifically to the target sequences (see again the Example at col 10-col 12; see also the definition of "probe" at col 2, lines 58-64). With further regard to step (a) of claim 1, Cronin et al disclose the labeling of target nucleic acid molecules with various types of labels (see, e.g., col 6, lines 12-35), and disclose general methods for detecting labeled molecules present on arrays (see col 7, line 55-col 9, line 55). Cronin et al also teach the use in their methods of light scattering labels including "gold, selenium, and titanium oxide" (see col 6, lines 27-29). However, Cronin et al teach that fluorescent labels are preferred for use in their methods (see col 3, lines 53-55), and Cronin et al do not disclose or exemplify the use of "scattered-light detectable particles" meeting the specific requirements of claim 1, step (a). Further, while Cronin et al teach the illumination of labels and detection of labeled molecules to achieve allele detection (see again col 7, line 55-col 9, line 55), Cronin et al do not specifically teach steps of illuminating scattered light detectable

particles or detecting light scattered by said particles, as set forth in steps (b) and (c) of claim 1.

Yguerabide et al disclose methods for the "ultrasensitive" detection of DNA target molecules, which methods use light scattering detectable particles in lieu of fluorescent labels and a "very simple and low-cost illumination system" employing white light (see entire reference, particularly page 137, right column, and page 154). Yguerabide et al also disclose that light scattering particles as employed in their methods are less susceptible to quenching and photodecomposition than are fluorescent labels (see page 155, right column). Yguerabide et al disclose the use of many different sizes and types of particles encompasses by the range set forth in claim 1, step (a); see, e.g., Tables 2, 3, and 4 at pages 150-151. Regarding claim 1, step (b), it is noted that it is a property of the illumination disclosed by Yguerabide et al that it is white light that "is not evanescent wave light," as required by the claims (for example, Yguerabide et al contrast their methods with a different technique employing light scattering labels and an evanescent wave illumination source at page 140, left column). Further, Yguerabide et al disclose that light scattered during their methods can be detected by the human eye without electronic amplification "at magnifications as low as 40X total magnification" (see page 140, left column).

In view of the teachings of Yguerabide et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cronin et al so as to have employed therein as labels the scattered-light detectable particles of Yguerabide et al, and to have employed therein

the illumination technique of Yguerabide et al, and thereby further to have practiced a method in which light scattering (rather than, e.g., fluorescence) is detected as an indicator of the presence of a particular allele. An ordinary artisan would have been motivated to have made such modifications to have achieved the advantages of ultrasensitive, simple and low cost detection, as taught by Yguerabide et al, and/or for the advantage of alleviating any problems related to quenching and/or photodecomposition occurring with the use of fluorescent labels, as suggested by Yguerabide et al.

With further regard to claim 2, it is noted that Cronin et al disclose the amplification of target nucleic acids prior to hybridization with probes (see, e.g., col 6, lines 2-13).

Regarding claim 3, 5, and 6, it is again noted that Cronin et al disclose labeled target molecules and arrays of unlabeled immobilized probes that capture the target molecules via hybridization (see entire reference, particularly col 5, line 59-col 7, line 54; col 9, lines 57-62).

With further regard to claims 5-6 and 70-71, it is again noted that Cronin et al disclose the differentiation of CYP2D6 alleles using different specific probes on an array (see the Example at col 10, line 47-col 11, line 20).

10. Claims 4 and 68-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al in view of Yguerabide et al as applied to claims 1-3, 5-6, and 70-71, above, and further in view of Service (Science 282:396-399 [October 1998]).

The teachings of Cronin et al and Yguerabide et al are set forth in paragraph 9, above. Cronin et al and Yguerabide et al do not teach a method comprising the use of probes labeled with scatter-light detectable particles, target nucleic acids that are not so labeled, and immobilized capture probes. Service discloses both methods in which labeled target nucleic acids are hybridized to arrays of unlabeled oligonucleotides (i.e., methods of the type suggested by Cronin et al in view of Yguerabide et al; see page 398, left and center columns) and an alternative array-based method for detecting specific sequences in which the target nucleic acid is unlabeled, and in which a third population of nucleic acids identified as "tagged" oligos are included in hybridization reactions to achieve determination of the sequence present in the target nucleic acid (see page 398, center column). Modification of the method suggested by Cronin et al in view of Yguerabide et al so as to employ unlabeled target nucleic acid in combination with a population of probes tagged with scattered-light detectable particles would have been obvious to one of ordinary skill in the art at the time the invention was made because it constitutes the mere substitution of one prior art array based detection method (as taught by Service) for another to achieve the predictable result of detecting the allele present in a sample.

11. Claims 9, 59-65, and 67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al in view of Yguerabide et al as applied to claims 1-3, 5-6, and 70-71, above, and further in view of Yguerabide et al (Analytical Biochemistry 262:157-176 [1998]; hereinafter referred to as "Yguerabide et al-II").

The teachings of Cronin et al and Yguerabide et al are set forth in paragraph 9, above. Regarding claim 9 and claims dependent therefrom, it is noted that Cronin et al disclose labeling target nucleic acid during amplification, and disclose the incorporation of various fluorescent labels (see col 6, lines 12-26). However, while Cronin et al and Yguerabide et al suggest the use of scattered-light detectable particles as labels (as discussed above), the references do not teach labeling "by incorporating a moiety that provides an attachment site and/or a cleavage site" (see text of claim 9), and further do not teach such labeling using any of the methods of claim 59. Further, the references do not teach embodiments wherein the incorporated moiety is "a modified nucleotide" (see claim 60), or a "hapten-derivatized nucleotide or bromodeoxyuridine" (claim 61), and do not teach the types of labels or "attaching" procedures of claims 62-65. The references also fail to teach labeling as required by claim 67, due to the failure to teach "an attachment site and/or a cleavage site" as set forth in claim 9 (from which claim 67 depends).

Like Yguerabide et al, Yguerabide et al-II disclose the use of scattered-light detectable particles as labels in sensitive detection methods employing white light illumination (see entire reference, particularly pages 164-165). Yguerabide et al-II disclose the incorporation of biotin into DNA molecules, and the attachment of scattered-light detectable particles coated with streptavidin, or coated with antibodies against any DNA-incorporated antigen, to such DNA (see page 174, right column). Yguerabide et al-II therefore suggest labeling DNA by incorporating into the DNA nucleotides derivatived with the hapten biotin, and the attachment of either streptavidin-

coated or antibody-coated detectable particles to such DNA, as set forth in the claims. It is noted that the biotin serves as an "attachment site" for streptavidin or for the specific antibody, such that the requirements of claim 9 are met. In view of the teachings of Yguerabide et al-II, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cronin et al in view of Yguerabide et al so as to have prepared target nucleic acids labeled with scattered-light detectable particles by incorporating into the nucleic acids (by PCR or any other well known method) biotin derivatized nucleotides, and by attaching to said nucleotides detectable particles labeled with either streptavidin or anti-biotin antibodies, as taught by Yguerabide et al-II. Such a modification of the method suggested by Cronin et al in view of Yguerabide et al would have been obvious to one of ordinary skill in the art because it constitutes the mere substitution of one type of prior art labeling method with another to achieve the predictable result of preparing labeled target nucleic acids Further, an ordinary artisan would have been motivated to have made such a modification in order to have prepared nucleic acids labeled with the type of label having the advantages taught by Yguerabide et al (rather than to have, e.g., experimented with various methods of preparing such molecules) for the advantage of more rapidly and efficiently preparing the nucleic acids needed for the methods suggested by Cronin et al in view of Yguerabide et al.

With further regard to claim 67, it is noted that Cronin et al disclose the use in amplification of primers that "flank the borders of a target polynucleotide of interest" (see col 6, lines 7-9), and that Cronin et al disclose and exemplify the detection of various

alleles of the CYP2D6 gene (see the example at col 10-col 12). Although Cronin et al do not disclose the labeling of CYP2D6 target nucleic acids using primers specific for the CYP2D6 gene, in view of Cronin et al's own teachings it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have employed such primers in the method suggested by Cronin et al in view of Yguerabide et al and Yguerabide et al-II in order to have achieved the predictable result of preparing appropriate, labeled target nucleic acids for use in the method.

12. Claims 61, 64, and 66 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cronin et al in view of Yguerabide et al and Yguerabide et al-II as applied to claims 9, 59-65, and 67, above, and further in view of Haider et al (Experimental Cell Research 234:498-506 [1997]).

This rejection applies to claims 61 and 64 to the extent that they may be limited to methods requiring bromodeoxyuridine and particles derivatized with anti-bromodeoxyuridine.

The teachings of Cronin et al, Yguerabide et al, and Yguerabide et al-II are set forth above in paragraph 11. With regard to the requirement in claim 66 that "said target nucleotide sequence is fragmented prior to hybridization with said nucleic acid probe," it is noted that the primary reference Cronin et al teaches that "The target is preferably fragmented before application to the chip to reduce or eliminate the formation of secondary structures in the target," and therefore discloses such a step and provides motivation to include it to achieve the advantages noted by Cronin et al. However, Cronin et al, Yguerabide et al and Yguerabide et al-II do not teach the incorporation of

bromodeoxyuridine into target nucleic acids, or the use of particles derivatived with anti-bromodeoxyuridine, as required by the claims.

Haider et al teaches that biotin-labeled nucleotides "are essentially limited to *in vitro* studies because of the poor penetrability of these molecules through the plasma membrane of live cells" (see entire reference, particularly page 498, right column) whereas BrdU labeled nucleotides may be successful employed both *in vivo* and *in vitro* (see page 499, left column). Haider et al also disclose the attachment of beads derivatized with anti-BrdU to nucleic acids containing BrdU (see page 499, left column and 500, left column), and teach that such nucleic acids may be successfully prepared by PCR and isolated using anti-BrdU coated beads (see page 499, left column, and page 500). In view of the teachings of Haider et al, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Cronin et al, Yguerabide et al, and Yguerabide et al-II so as to have employed therein BrdU in lieu of biotin and scattered-light detectable particles labeled with anti-BrdU in lieu of such particles labeled with streptavidin or anti-biotin. Such a modification would have been obvious to one of ordinary skill in the art because it constitutes the mere substitution of one type of prior art labeling method with another to achieve the predictable result of preparing labeled target nucleic acids Further, an ordinary artisan would have been motivated to have made such a modification in order to have prepared nucleic acids having the advantages taught by Haider et al, specifically, for example, nucleic acids that could be prepared *in vivo* rather than *in vitro*

in such instances when such a preparation method was more convenient for a practitioner.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Diana B. Johannsen whose telephone number is 571/272-0744. The examiner can normally be reached on Monday and Thursday, 7:30 am-4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached at 571/272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Diana B. Johannsen
Primary Examiner
Art Unit 1634